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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

HANLEY, SUSAN MARIE

ART UNIT

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1651

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05/20/2010

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/582,794	Applicant(s) NORRILD ET AL.	
	Examiner SUSAN HANLEY	Art Unit 1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 25 January 2010.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 33-69 is/are pending in the application.
- 4a) Of the above claim(s) 55-64 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 33-54 and 65-69 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|-------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>12/28/2009</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Claims 33-69 are pending.

Election/Restrictions

Applicant's election of Group I, the reagent claims of 33 to 54, is again acknowledged. The specie elections for the reagent were withdrawn. The reagent claims (33-54 and 65-69) remain restricted from the process claims (61-63), the dye claims (55-60) and the complex claim (64) due to lack of unity since the reagent, as claimed, is known in the prior art (see the 103 rejection below). Thus, claims 55-64 stand withdrawn.

Claims 33-54 and 65-69 are under examination.

Withdrawal of Rejections

Applicant's arguments, filed 01/25/2010, have been fully considered regarding previous rejections and they are fully persuasive. Rejections and/or objections not reiterated from previous Office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112

Claims 33-54 and 65-69 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 33 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such

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omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural cooperative relationships are: The energy acceptor comprises a trityl structure that has a positive charge. A moiety having a positive charge must have a moiety having a negative charge to be electrically neutral. The missing structural element is a moiety with a negative charge.

Claim 42 is rejected because the concept of a linkage lacks antecedent basis in claim 33.

Claim 45 is rejected because it is vague. The claim recites values for R^1 to R^3 optional substituted with one or more substituents. It is unclear if only the last R^1 to R^3 value (methylethylamino) is optionally substituted with the named functional groups or if dimethylamino, dimethylamino and methylethyl amino are all optionally substituted with the named functional groups.

Claim 50 is rejected because it is confusing. The claim recites the following ions: " Li_3^+ , Na_3^+ , K_3^+ and Mg_3^+ ". Ions of lithium, sodium and potassium are single ionic entities each having a single positive charge. There are no such compounds of ions having three lithiums, three potassiums or three sodiums with a single positive charge. Likewise, an ion of magnesium is a single ionic entity having a +2 charge. There is no such compound having of ions having two magnesiums with a +2 charge. Furthermore, the reagent of claim 33 has a positive charge. A counterion to it must have a negative charge. The recited ions having a positive charge are not consistent with electrical neutrality.

Claims 34-41, 43, 44, 46-49, 51-54 and 65-69 are rejected because they are dependent claims that do not overcome the deficiencies of the rejected independent claim from which they depend.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 33, 37-41, 43, 44 and 50-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cote et al. (US 6,485,703; "Cote") and Lu et al. (US 20020102267; "Lu"; evidence document) in view of Thurmond et al. (US 20040259206; "Thurmond"), Owen et al. (1972): "Owen"), the STN Registry file print out for Crystal Violet and Matzuk (WO 89/09833; cited in the IDS filed 06/14/2006).

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Cote discloses an assay for glucose based on fluorescence resonance energy transfer (FRET). Concanavalin A (Con A) is linked via a succinyl linker to an energy acceptor tetramethyl rhodamine isothiocyanate (TRITC). Fluorescein isothiocyanate (FITC) is linked to dextran, a glucose analog. In the absence of glucose, TRITC-succinyl-Con A binds to FITC-dextran and FITC fluorescence is quenched. As glucose binds to TRITC-succinyl-Con A, FITC-dextran is liberated. The resulting increase in fluorescence is proportional to the concentration of glucose. Any dye pair that results in FRET is acceptable for the assay. Established protocols for conjugating FITC and TRITC with polysaccharides and Con A lysine are known by those of ordinary skill in the art (col. 21, lines 15-35).

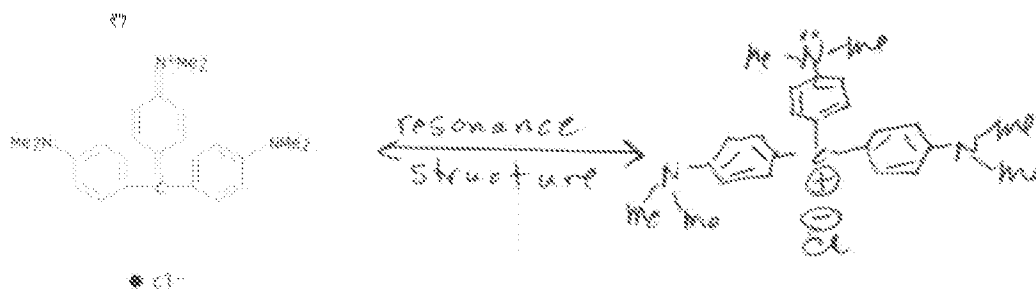
Lu discloses that Concanavalin A is a lectin ([section 0395]). Lu is cited as an evidence document.

This disclosure meets, in part, the limitations of instant claim 33 wherein a reagent having a energy donor and an energy acceptor undergo FRET when they are sufficiently close together. The limitation of instant claim 37 is met since the energy donor and energy acceptor are linked by non-covalent binding (dextran non-covalently binds to Con A). The analyte binding agent, Con A, is a lectin (instant claim 39). The analyte analog is dextran, a glucose analog (instant claims 40 and 41). The limitations of instant claim 38 are met since the binding of glucose, the analyte, disrupts the FRET interaction causing the distance between the energy acceptor and the energy donor to increase.

Cote does not teach that the energy acceptor is a triphenylmethane cation having the structure shown in instant claim 33.

Thurmond discloses that triphenylmethanes are suitable quenchers in a FRET assay (section [0080]).

Owen teaches that Crystal Violet (CV) can quench the fluorescence of fluorescein (page 1045, section 3.1, Figure 1). From the printout from the Registry file of crystal violet, one can see that the resonance structure of CV



meets the limitations of the triphenylmethane energy acceptor of the formula recited in instant claim 33. The counter ion for the CV is chloride, a halide, as in instant claim 50.

Matzuk discloses the triphenylmethane dye Doebner's Violet (page 24):

Doebner's Violet



· which has two primary amine groups.

Matzuk reports that Doebner's Violet is an energy acceptor, p. 15-16). The structure of Doebner's Violet meets the limitations of the structure of claim 33 since Doebner's Violet comprises a triphenylmethane rings structure wherein R¹- to R³ are electron donating substituents (amino, also meeting instant claim 44) and the remaining R groups are hydrogen.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute Doebner's Violet for TRITC as the energy acceptor. The ordinary artisan would expect that CV and Doebner's Violet would have similar absorbance spectra since the structure of the energy accepting moieties is the same (e.g., the energy accepting moieties for the compounds are the aryl rings). Hence, Doebner's Violet and CV are functionally equivalent energy absorbers. The ordinary artisan would have been motivated substitute Doebner's Violet for TRITC because each energy acceptor is known to have the same function, accepting energy from a fluorescent energy donor. Hence, the substitution is no more than the predictable use of prior art elements according to their established functions resulting in the simple substitution of one known element for another for a predictable result. The ordinary artisan would have had a reasonable expectation that one could substitute Doebner's Violet for TRITC as the energy acceptor since CV, which has the same triaryl structure as Doebner's Violet, is known to quench the fluorescence of fluorescein. The ordinary artisan would have had a reasonable expectation that one could attach Doebner's Violet to succinyl-Con A since primary amines (nucleophiles) react with succinyl esters. This disclosure meets the limitations of claims 43 and 51 wherein there is a linker structure at R³ wherein an amine reacts through an active ester and the reaction partner is a protein (Con A, instant claim 52).

Claims 33, 37-41, 43, 44, 50-52 and 54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cote et al. (US 6,485,703; "Cote") and Lu et al. (US

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20020102267; "Lu") in view of Thurmond et al. (US 20040259206; "Thurmond"), Owen et al. (1972): "Owen"), the STN Registry file print out for crystal violet and Matsuki (WO 89/09833; cited in the IDS filed 06/14/2006), as applied to claims 33, 37-41, 43, 44 and 50-52, in further view of Whitson et al. (Analytical Biochemistry; available on-line 11/27/03) and the STN Registry Print out for Alexa Fluor 594.

The combined disclosure of Cote, Lu, Thurmond, Owen, STN and Matsuki are discussed supra.

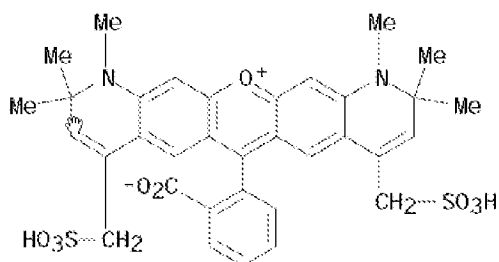
The combined disclosures do not teach that the energy donor absorbs light at 594 nm and fluoresces at 620 nm (instant claim 54).

Whitson teaches the preparation and characterization of Alexa Fluor 594, an energy donor, for FRET studies with epidermal growth factor receptor. Alexa Fluor absorbs light at 594 nm and fluoresces at 620 nm (Fig. 3, page 231). Alexa Fluor 594 was successfully employed as the energy donor to study EGF-EGF receptor interactions (abstract). Alexa Fluor 594 was attached to EGF via a succinimide linker.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute Alexa Fluor 594 for the energy donor in the glucose assay of the combined references wherein Doebner's Violet is the energy acceptor. The ordinary artisan would have been motivated to do so because each energy donor (FITC and Alexa Fluor 594) is known to have the same function, acting as a fluorescent energy donor. Hence, they are functional equivalents. Therefore, the substitution is no more than the predictable use of prior art elements according to their established functions resulting in the simple substitution of one known element for another for a

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predictable result. The ordinary artisan would have had a reasonable expectation that one could substitute Alexa Fluor 594 for FITC and that Doebner's Violet would quench the fluorescence of Alexa Fluor because the absorbance spectrum for CV (and hence Doebner's Violet) overlaps the fluorescence emission spectrum for Alexa Fluor 594 which is necessary for the energy transfer process. The ordinary artisan would have had a reasonable expectation that one could attach Alexa Fluor 594

D1-CO₂H

to dextran because it has reactive

moieties (carboxylate and sulfonyl groups) that can react with bifunctional linkers for conjugation with dextran. Conjugation is well within the purview of the ordinary artisan, a synthetic chemist.

Claims 33, 37-41, 43, 44 and 50-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cote et al. (US 6,485,703; "Cote") and Lu et al. (US 20020102267; "Lu") in view of Thurmond et al. (US 20040259206; "Thurmond"), Owen et al. (1972): "Owen"), the STN Registry file print out for crystal violet and Matzuk (WO 89/09833; cited in the IDS filed 06/14/2006), as applied to claims 33, 37-41, 43, 44 and 50-52, in further view of Aldrich Catalog (1996, page 1352).

The combined disclosure of Cote, Lu, Thurmond, Own, STN and Matzuk are discussed supra.

The combined disclosures do not teach that the linker between the energy acceptor and the Con A is succinimide (instant claim 53).

Aldrich Catalog teaches that succinic anhydride and succinimide differ only by the linkage between the two carbonyl groups (page 1352). Succinic anhydride has an oxygen and succinimide has a nitrogen. The ordinary artisan would have known that the reaction of either compound would produce a succinyl linking group since primary amine like those of Doeber's Violet react with cyclic esters and cyclic amides. Hence, succinyl anhydride and succinimide are functional equivalents since they yield the same linker structure. Hence, it would have been obvious to substitute succinimide for the linker element between Doeber's Violet and Con A in the reagent disclosed by the combined references. The ordinary artisan would have been motivated to do so because succinic anhydride and succinimide are known to have the same function, acting as linkers to produce succinyl linking groups. Hence, the substitution is no more than the predictable use of prior art elements according to their established functions resulting in the simple substitution of one known element for another for a predictable result. The ordinary artisan would have had a reasonable expectation that one could substitute succinimide for succinyl anhydride to make the succinyl linker between Doeber's Violet and Con A since amines react with cyclic amides.

Claims 33-36 and 50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Burroughs-Tencza (US 20030166028) view of Thurmond et al. (US 20040259206; "Thurmond"), Owen et al. (1972): "Owen"), the STN Registry file print out for crystal violet and Matsuk (WO 89/09833; cited in the IDS filed 06/14/2006).

Burroughs-Tencza discloses a protease biosensor that detects lethal factor from *Bacillus anthracis* comprising a peptide having an amino acid sequence wherein a fluorescent donor molecule and an energy acceptor molecule are attached to the peptide on opposite ends of the cleavage site of the peptide. FRET occurs in the absence of the protease. In the presence of the protease, cleavage of the peptide results in separation of the two fluorophores and the loss of FRET. Thus the biosensor functions by reporting the activity of a protease by change in FRET between the two fluorophores separated by the protease cleavage sequence (section [0014] to [0023]). The donor and acceptor fluorophores are selected as a matched pair wherein the absorption spectrum of the acceptor molecule significantly overlaps the emission spectrum of the donor molecule. One preferred pair is fluorescein as the donor and rhodamine, eosin, erythrosin or an Alexa Fluor as the acceptor (section [0084]).

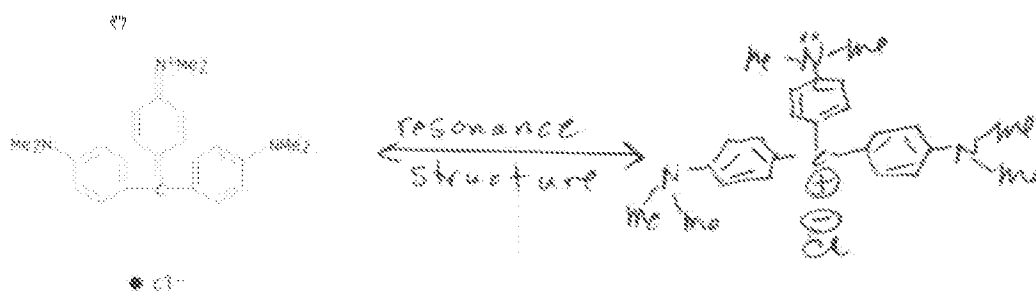
This disclosure meets, in part, the limitations of instant claim 33 wherein a reagent having a energy donor and an energy acceptor undergo FRET when they are sufficiently close together. The limitation of instant claim 34 is met since the energy donor and energy acceptor are linked by covalent bonding. When the peptide is cleaved the distance between the energy donor and the energy acceptor increases (instant claim 35). The energy donor and the energy acceptor are linked by a polypeptide

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sequence (instant claim 36) that modulates the FRET interaction of the acceptor/donor pair.

Thurmond discloses that triphenylmethanes are suitable quenchers in a FRET assay (section [0080]).

Owen teaches that Crystal Violet (CV) can quench the fluorescence of fluorescein (page 1045, section 3.1, Figure 1). From the printout from the Registry file of crystal violet, one can see that the resonance structure of CV



meets the limitations of the triphenylmethane energy acceptor of the formula recited in instant claim 33. The counter ion for the CV is chloride, a halide, as in instant claim 50.

Matzuk discloses the triphenylmethane dye Doebner's Violet (page 24):

Doebner's Violet



· which has two primary amine groups.

Matzuk reports that Doebner's Violet is an energy acceptor, (p. 15-16). The structure of Doebner's Violet meets the limitations of the structure of claim 33 since Doebner's Violet comprises a triphenylmethane rings structure wherein R¹- to R³ are electron donating substituents (amino, also meeting instant claim 44) and the remaining R groups are hydrogen.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute Doebner's Violet for any of the energy acceptors taught by Burroughs-Tencza. The ordinary artisan would expect that CV and Doebner's Violet would have similar absorbance spectra since the structure of the energy accepting moieties is the same (e.g., the energy accepting moieties for the compounds are the aryl rings). Hence, Doebner's Violet and CV are functionally equivalent energy acceptors. The ordinary artisan would have been motivated substitute Doebner's Violet for any of the energy acceptors taught by Burroughs-Tencza because each energy acceptor is known to have the same function, accepting energy from a fluorescent energy donor. Hence, the substitution is no more than the predictable use of prior art elements according to their established functions resulting in the simple substitution of one known element for another for a predictable result. The ordinary artisan would have had a reasonable expectation that one could substitute Doebner's Violet for any of the energy acceptors taught by Burroughs-Tencza as the energy acceptor since CV, which has the same triaryl structure as CV, is known to quench the fluorescence of fluorescein. The ordinary artisan would have had a reasonable expectation that one could attach Doebner's Violet to the peptide sequence since primary amines (nucleophiles) react with amide groups.

Claims 33 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hugl et al. (US 5,194,393; cited in the IDS filed 12/28/09) view of Thurmond et al.

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(US 20040259206; "Thurmond"), Owen et al. (1972): "Owen"), the STN Registry file print out for crystal violet and Matsuk (WO 89/09833; cited in the IDS filed 06/14/2006).

Hugl discloses a sensor comprising a solid support to which a Langmuir-Blodgett (LB) film is attached to the surface and has at least one fluorescent energy donor attached therewith. A first receptor molecule is either bonded covalently to the film or absorbed onto the film. A second receptor is covalently bound to another dye whose excitation band overlaps with that of the donor fluorophore. The second receptor binds to the first receptor in the presence of an analyte (col. 2, lines 50 through col. 3, line 10, the second alternative (e2) and claim 1 of the patent). The donor molecule can be any of dyes IVa to IVk which include dye IVj a fluorescein dye. This disclosure meets the limitations of claim 33 and 42 in part because a reagent system comprising an energy donor and energy acceptor are complexed in the presence of an analyte. Since the complex occurs in the presence of the analyte, FRET occurs, as in instant claim 42. The selection of dye IVj is easily envisaged since it is a member of a small genus (11 dyes).

Hugl does not teach that the acceptor dye is Doebner's Violet.

The disclosures by Thurmond, Owen, the STN Registry file print out for Crystal Violet and Matsuk are discussed supra.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ Doebner's Violet as the energy acceptor in the reagent system of Hugl. The ordinary artisan would have been motivated to do so because Doebner's Violet is an energy acceptor that has an emission spectrum that overlaps with that of fluorescein thus allowing for FRET when it is in close proximity with a

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fluorescence energy acceptor. The ordinary artisan would have had a reasonable expectation that one could employ Doebner's Violet as the energy acceptor in the reagent system taught by Hugi since it has the same triaryl structure as Crystal Violet, which is known to quench the fluorescence of fluorescein. The ordinary artisan would have had a reasonable expectation that one could attach Doebner's Violet to a receptor since it has primary amines (nucleophiles) that are reactive with bifunctional linkers. Conjugation is well within the purview of the ordinary artisan.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SUSAN HANLEY whose telephone number is (571)272-2508. The examiner can normally be reached on M-F 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Susan Hanley/
Examiner, Art Unit 1651